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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,104	04/05/2005	Sui Xiong Cai	1735.0760002/RWE/RAS	5087

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EXAMINER	
KUDLA, JOSEPH S	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
12/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,104	CAI ET AL.	
	Examiner	Art Unit	
	Joseph S. Kudla	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21,23 and 25* is/are pending in the application.

4a) Of the above claim(s) *20,22,24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 21, 23 and 25* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Cbz-Val-Asp-CH_2F in the reply filed on 9/26/05 is acknowledged. The traversal is on the ground(s) that cited publication by Choong et al. (US PG Pub 2003/0114447) did not teach the use of a caspase inhibitor to treat, ameliorate or prevent a disease caused by exposure to radionuclides, biological agents or chemical agents. This is not found persuasive because Choong et al teaches the treatment of acute alcoholic hepatitis (page 20, line 3) with a caspase inhibitor. Acute alcoholic hepatitis occurs after acute alcohol ingestion, therefore, Choong et al does teach the use of a caspase inhibitor to treat a disease caused by exposure to a chemical agent. Furthermore, Applicant, to satisfy the requirements imposed by the restriction, was required to identify the claims readable on the elected compound and withdraw those that are not readable on the elected compound from examination. As such, the examiner withdraws claims 20, 22, 24 and 26 from consideration for not reading on the elected compound.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. This application is a 371 of PCT/US2003/010645 (filed April 7, 2003), which claims benefit of US Provisional Application No. 60/369,806 (filed April 5, 2002). Priority to April 5, 2002 is acknowledged.

Claim Objections

3. Claim 12 is objected to because of the following informalities: The parenthetical around the word "Yersinia pestis" excludes the word "Yersinia pestis". If applicant seeks inclusion of the word the "Yersinia pestis", please remove parenthetical. If the word "Yersinia pestis" is meant as an example of the word plague, then the word "Yersinia pestis" should be cancelled as well due to the disclosure on page 15, last line.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 5-19, 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 5-19, 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification while providing enablement for showing an improvement in survival rate of mice by the administration of an intravenous injection of a caspase inhibitor, Cbz-Val-Asp-Ch_2F, after what was established by Applicant as a lethal dose of ^{137}Cs does not reasonably provide enablement for protecting against chemical and biological exposure, does not provide support for an effective dosage administration route, has not shown the caspase inhibitor to be effective when administered prior or during an exposure event and has not shown unintentional exposure from a nuclear power plant, research facility, etc. or intentional exposure from a bomb or a spill. Furthermore, Applicant has not reasonably provided support for the only compound tested on the mice, Cbz-Val-Asp-Ch_2F, works via the mechanism of action for which Applicant purports, reduction in cell death, specifically in the gastrointestinal tract, skin, hair, bone marrow, immune system, nervous system or liver. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation to treat, ameliorate or prevent a disease or condition by exposure to radionuclides, biological agents or chemical agents via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited as outlined in the claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on

the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is extremely broad with relation to the ability of caspase inhibitors being able to treat, ameliorate or prevent a disease or condition by exposure to radionuclides, biological agents or chemical agents via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited. Applicant has also claimed that the inhibition of such cell death could be reduced across many tissues such as tissues of the gastrointestinal tract, skin, hair, bone marrow, immune system, nervous system or liver. Applicant also has claimed the caspase inhibitors to be useful in a wide range of events such as a chemical spill, a bomb, a mishap at a research facility or hospital, etc.

The nature of the invention

Claim 1 is directed to caspase inhibitors being able to treat, ameliorate or prevent a disease or condition by exposure to radionuclides, biological agents or chemical agents via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited. Claim 2 indicates the tissues where cell death occurs. Claims 3-5 indicate the administration routes. Claims 6-7 indicate the incidents where the exposure events might occur. Claims 10-13 indicate the biological, radionuclide and chemical agent examples. Claims 14-16 indicate when the compound is to be administered. And claims 17-19, 21, 23 and 25 indicate the compounds Applicant purports to be useful as caspase inhibitors.

The state of the prior art

The state of the prior art is enabling for demonstrating that caspase inhibitors can slow the rate of cell death. However, Applicant has not demonstrated through prior art or in the instant disclosure the ability of the compounds indicated in the claim set to be able to inhibit cell death through the mechanism of being an inhibitor of caspase.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Many compounds exist in the art that are capable of performing as a caspase inhibitor, but at the time of invention only a few had been tested *in vitro* against chemical agents and radiation and no studies have been shown *in vivo*. Due to the unpredictability in the pharmaceutical art, it

is noted that the invention is required to be assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity. Studies conducted by the Applicant as indicated in the specification in examples 1, experiment B shows that fewer mice died as a result of the administration of the compound, Cbz-Val-Asp-Ch_2F, at levels of γ-radiation determined lethal by Applicant's work in experiment A. However, Applicant has failed to elucidate if the compound is working via the mechanism of action which Applicant claims. Without this background information, one could not predict if the compound was in fact functioning in the manner Applicant asserts. In addition, without test data or reference from prior art, it is impossible to predict if administration prior or during an exposure event would be capable of having an effect, due to unknown clearance rates of the compounds in the subject. Furthermore, the assertion of the ability to inhibit cell death during a chemical agent or biological agent exposure event, without actually conducting testing or referencing prior art to the fact for the compounds of interest, makes practicing the invention unpredictable. And lastly, without actually determining if oral or topical administration is actually effective through prior art or Applicant's own work, it would be unpredictable if the compounds would be effective at treating an exposure event. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. *In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970)*, indicates that the more unpredictable an area is, the more specific enablement is necessary in

order to satisfy the statute. Hence, one of skill in the art is unable to fully predict possible results from the administration of the compound.

The amount of direction provided by the Applicant and The existence of working examples

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant provides limited guidance regarding the use of the instant elected compound (and no guidance of any other claimed caspase inhibitor) in treating, ameliorating or preventing a disease or condition by exposure to radionuclides via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited. Example I, experiment B, shows that the compound, Cbz-Val-Asp-Ch_2F, has some effect at reducing lethality in mice when the mice are subjected to γ- radiation, but the results and the remainder of the instant specification are silent on the specific tissues effected and whether cell death is inhibited in them, as well as, by which mechanism of action. Applicant provides no guidance on treating, ameliorating or preventing a disease or condition by exposure to biological agents or chemical agents via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited. Applicant provides no guidance on exposure events where the radionuclide, biological agent or chemical agent originates from an exposure event from such events or places like a nuclear power plant, a bomb, a spill, a manufacturing or processing plant and a hospital.

The specification provides no direction or guidance for determining the administration route and it's effectiveness. With no results, it is difficult to envision that the compounds instantly claimed can inhibit cell death via administration of a caspase inhibitor.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (*In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993)*). The specification lacks sufficient disclosure to support applicant's claims. There is not seen sufficient working examples or data from references on the prior art providing a nexus between that which applicant asserts as proof of the claimed method.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art, and the breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation. Reasonable guidance with respect to treating, ameliorating or preventing a disease or condition by exposure to radionuclides, biological agents or chemical agents via the administration of a caspase inhibitor to an animal such that cell death in the subject is inhibited has not been enabled by the instant disclosure. Without such, one of ordinary skill in the art would have to perform an inordinate amount of repeated testing with each compound Applicant claims on different

radionuclides, biological agents or chemical agents to determine their effectiveness in treating a subject.

5. Claims 1-19, 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The use of the terminology "of preventing" in the first line of claim 1 is contentious.

To prevent, as defined by Merriam-Webster Dictionary is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the definition of "to prevent" and the "act of preventing" embraces the complete 100% inhibition. Thus, the burden of enablement in the assertion of this claim is much higher than would be the case of enabling the treatment of the condition and is not achieved. The instant application enables a moderate reduction in the number of mice when the caspase inhibitor, Cbz-Val-Asp-CH_2F is administered. That being stated, nowhere in the art or instant application has the efficacy of the caspase inhibitor, Cbz-Val-Asp-CH_2F, been enabled to prevent or completely control apoptosis and subsequent death of the subject.

Appropriate correction is required

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-5, 8 and 14-19 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Weber et al (WO 01/27140, cited by Applicant).

Weber et al teaches the use of a caspase inhibitor to treat, ameliorate or prevent bone marrow cell death in an animal via administering a caspase inhibitor (Claim 1). Weber et al teaches topical or oral administration (claim 2) or injection (claim 11) and a pharmaceutical composition with an acceptable carrier (claim 12). Weber et al teaches the intentional administration due to chemotherapy (claim 1). Weber et al teaches the administration of the caspase inhibitor prior, during or after the exposure event (claims17-19). Weber et al teaches various caspase inhibitor compounds (claims 13-16) which includes the compound Cbz-Val-Asp-CH_2F (claim 14, line 3).

Art made of record and but not relied upon

7. Cai et al (US 2004/0116355, US 2002/0058631, US 6,716,818 and US 6,355,618 (cited by applicant)), Choong et al (US 2003114447) and Wang et al (US 6,495,522 (cited by applicant)).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph S. Kudla whose telephone number is (571) 270-3288. The examiner can normally be reached on 9am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JK

Ardin H. Marschel 12/17/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER